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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/855,587	05/16/2001	Yoshiki Sasai	766.44	1416

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FITZPATRICK CELLA HARPER & SCINTO
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

EXAMINER

SGAGIAS, MAGDALENE K

ART UNIT	PAPER NUMBER
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1632

MAIL DATE	DELIVERY MODE
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10/04/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.		Applicant(s)	
	09/855,587		SASAI ET AL.	
	Examiner		Art Unit	
	Magdalene K. Sgagias		1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 August 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 15, 18-21, 23, 24, 72, 74, 75 and 80-87 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 15, 18-21, 23-24, 72, 74-75, 80-87 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/17/07 has been entered.

Applicant's arguments filed 8/17/07 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1, 15, 18-21, 23-24, 72, 74-75, 80-87 are pending and under consideration. Claims 2-14, 16-17, 22, 25-71, 73, 76-79 are canceled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 15, 18-21, 23-24, 72, 74-75, 80-87 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The present claims have been amended to recite and encompass a method that has culturing an embryonic stem cell in vitro (i) in the absence of retinoic acid and (ii) in the presence of a stroma cell recognized by a monoclonal antibody produced by hybridoma FERM BP-7573 without forming embryoid body for a time period from 1 day to 14 days and then

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culturing continuously the cell in vitro (iii) in the absence of retinoic acid and (iv) in the presence of both BMP-4 and a stroma cell recognized by a monoclonal antibody produced by hybridoma FREM BP-7573 without forming embryoid body. Literal support for these steps and what is accomplished by these steps cannot be found in the specification. Moreover, figurative support for these steps, wherein it results in "differentiation of an embryonic stem cell into a neural crest cell or a neural tube cell" cannot be found and appears to be inconsistent with the teachings of the present specification. More specifically, it appears the BMP-4 in the absence of retinoic acid is affecting the embryonic stem cell to differentiate preferentially into neural cell lineage. The method steps in examples 1 or 2 of the specification, wherein EB5 embryonic stem cells differentiate into neuronal cells expressing neural specific markers or into non-neuroectodermal cells respectively, so not support the production of a neural crest cell or a neural tube cell. Moreover, the method steps of example 14, wherein differentiation induction of embryonic stem cell into neural cells expressing the various neural markers as shown in Table 1 of example 14, do not support the production of a neural crest cell or a neural tube cell by way of the claimed methods. More specifically in example 14, EB5 cells were precultured for 4 days before the addition of BMP-4. It is noted that the Applicants fail to point to any specific support for the present claim amendments.

MPEP 2163.06 notes "If new subject matter is added to the disclosure, whether it be in the abstract, the specification, or the drawings, the examiner should object to the introduction of new matter under 35 U.S.C. 132 or 251 as appropriate, and require applicant to cancel the new matter. If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981). The examiner should still consider the subject matter added to the claim in making rejections based on prior art since the new matter rejection may be

overcome by applicant. In an instance in which the claims have not been amended, per se, but the specification has been amended to add new matter, a rejection of the claims under 35 U.S.C. 112, first paragraph should be made whenever any of the claim limitations are affected by the added material. When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

To the extent that the claimed methods are not described in the instant disclosure, claims 1, 15, 18-21, 23-24, 72, 74-75, 80-87 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention since a disclosure cannot teach one to make or use something that has not been described.

The specification teaches the term "cell of neural tube" means a cell which constitutes a neural tube in the generation process of neural tube in the initial stage of development in chodrates [0192] and the term "cell of neural crest:" means a cell which constitutes a neural crest in the above generation process [0193]. However, applicants failed to provide guidance to correlate the induction of differentiation of embryonic stem cells into neural cell expressing neural surface markers into a neural crest cell or a neural tube cell that morphologically, physiologically or structurally meets the limitations of a neural tube or a neural crest cell. The mere expression of neural surface markers on the differentiated embryonic stem cells of the disclosed invention cannot support the morphological, structural and physiological limitations of these cells in the generation process of a neural crest or neural tube. **Mizuseki et al**, (PNAS,

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100(10): 5828-5833, 2003) notes it remains to be known whether ES cell-derived neural precursors generated in vitro can produce the full dorsal-ventral range of neuroectodermal derivatives in response to embryonic positional information (p 5828, 1st column, 3rd paragraph). Further, the instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of producing the full dorsal-ventral range of neuroectodermal derivatives in response embryonic positional information raised by the state of the art. Therefore, the skilled artisan would conclude that the state of art of producing neural crest cell or neural tube cell is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for producing these cells without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the specific steps for the production of a neural crest cells or neural tube cell with the structural, functional and morphological characteristics of said cells, the lack of direction or guidance provided by the specification to determine the specific steps for the production of a neural crest cells or neural tube cell, the absence of working examples that correlate the induction of differentiation of embryonic stem cells into neural cells expressing neural surface markers to the production of neural crest cells or neural tube cells, the unpredictable state of the art with respect to the production of a neural crest cells or neural tube cell, the undeveloped state of the art pertaining to the production of a neural crest cells or neural tube cell, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Applicants argue the claims have been amended in order to recite the present invention with specificity required by statute. Applicants argue that the examiner objected to the Applicants' use of "wherein" clauses.

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These arguments are not persuasive because the amendments have not recited the specific method steps for the production of the claimed cells by way of the claimed methods. As discussed above the specification teaches the differentiation of embryonic stem cells into neural cells expressing neural cell surface markers. The expression of neural cell surface markers cannot be correlated to the structure and function and morphological limitations of a neural crest cell or a neural tube cell, which is produced during the neural tube generation as discussed above. With regard to the clause "wherein" the examiner meant that the interpretation of this clause simply does not limit the inclusion of any stromal cell, which is recognized by a monoclonal antibody produced by hybridoma FERM BP-7573 however, the method steps as claimed cannot be found in the specification for the production of claimed cells.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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Magdalene K. Sgagias, Ph.D.

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/Anne-Marie Falk/
Anne-Marie Falk, Ph.D.
Primary Examiner, Art Unit 1632